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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,296	03/21/2001	Laura L. Kiessling	1-00	4642

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EXAMINER	
SHIBUYA, MARK LANCE	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 03/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,296	KIESSLING ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/13/2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *43,61,63,65,69,70,89 and 156* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☒ Claim(s) *161* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/29/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 17,20-23,28-30,41-43,59-61,63-65,68-74,82,89-92,140-148 and 150-164.

Continuation of Disposition of Claims: Claims rejected are 17,20-23,28-30,41,42,59,60,64,68,71-74,82,90-92,140-148,150-155,157-160 and 162-164.

DETAILED ACTION

1. Claims 17, 20-23, 28-30, 41-43, 59-61, 63-65, 68-74, 82, 89-92, 140-148, 150-164 are pending. Claims 43, 61, 63, 65, 69, 70, 89, 156 are withdrawn from consideration. Claim 161 is objected to. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 82, 90-92, 140-148, 150-155, and 157-160 and 162-164 are examined.

Allowable Subject Matter

2. The indicated allowability of claims 145-147 is withdrawn. Rejections of said claims, based on 35 U.S.C. § 112, first paragraph, follow.

Withdrawn Claim Rejections

3. The rejection of Claims 1, 2, 3, 17, 19, 21, 22, 30, 59, 60, 62, 68, 81, 82, 85, 86, 90, 91, 95, 142, 143, 144, under 35 U.S.C. § 102(a) as being anticipated by Gordon et al., (Chemistry & Biology, vol. 7:9-16, 2000), is withdrawn in view of applicant's amendments to the claims.

4. The rejection of Claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 82, 83, 90-92, 94, 95 140-143, 151, 154, 155, 157 under 35 U.S.C. § 102(b) as being anticipated by Whitesides et al., WO 98/46270 (reference 4, IDS filed 10/10/2002), is withdrawn in view of applicant's amendments to the claims.

5. The rejection of Claims 1, 81, 82, 83, 85, and 90 under 35 U.S.C. § 102(e) as being anticipated by Kiessling et al., US 6,291,616, (reference 1, IDS filed 10/10/2002), is withdrawn in view of applicant's amendments to the claims.

6. The rejection of Claims 1-3, 59, 60, 62, 64, 68, 74, 81, 82, 83, 90, 91, 92, 144, and 157 are rejected under 35 U.S.C. 102(a) as being anticipated by Arimoto et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11), is withdrawn in view of applicant's amendments to the claims.

7. The rejection of Claims 1-3, 17, 28, 29, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90, 91, 142, 144, 152 and 157 under 35 U.S.C. 102(b) as being anticipated by Kanai et al., J. Am. Chem. Soc, 1997, Vol. 119 (41), pp. 1361-1362, (IDS filed 10/10/2002, ref. 45), is withdrawn in view of applicant's amendments to the claims.

8. The rejection of Claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90-92, 94, 95, 140-143, 144, **148**, **149**, 151, 154, 155, 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al., WO 98/46270 (reference 4, IDS filed 10/10/2002); and Arimoto et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11), is withdrawn in view of applicant's amendments to the claims.

9. The rejection of Claims 1-3, 17, 18, 19, 20-23, 28-30, 41, 42, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90-92, 94, 95, 140-143, 144, 148, 149, 151, 154, 155, 157 under 35 U.S.C. 103(a) as being unpatentable over **Whitesides et al.**, WO 98/46270 (reference 4, IDS filed 10/10/2002), **Arimoto et al.**, Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11), and further in view of **Truett**, US 6,437,119 B1, is withdrawn in view of applicant's amendments to the claims.

10. The rejection of Claims 1-3, 17, 28, 29, 59, 60, 62, 64, 68, 71-74, 81, 82, 83, 90, 91, 142, 144, 152, **153** and 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Kanai et al.**, J. Am. Chem. Soc, 1997, Vol. 119 (41), pp. 1361-1362, (IDS filed 10/10/2002, ref. 45) and **Kaplan et al.**, J. Immunol. Methods 20: (1997) 15-24, (IDS filed 10/10/2002, reference 46), and further in view of **Truett**, US 6,437,119 B1, is withdrawn in view of applicant's amendments to the claims.

Election/Restrictions

11. Claim 28 is drawn to two species of signal recognition elements that are N-formyl peptide and N-acyl peptide. Applicant's elections, with traverse, including the species of N-formyl peptide, in the Response, entered 3/4/2004, are maintained. The Requirement for Restriction/Election, mailed 9/4/2003, is maintained.

Priority

12. This application claims benefit of 60/191,014, filed 3/21/2000.

Information Disclosure Statement

13. The IDS, entered 8/29/2005, has been considered.

Claim Objections

14. Claim 161 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 161 drawn to a method wherein Z is OH, depends from claim 158; however claim 158 does not recite a limitation to Z.

Maintained and New Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 82, 90-92, 140, 142, 143, 148, 150-155, 157, and 162-164 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for new matter.

The specification as filed does not appear to provide support for methods comprising signal recognition elements that are an N-formyl peptide or an N-acyl peptide, which induces the release of an intracellular signal. Applicant must point, with particularity, where support for this limitation may be found in the specification as filed.

16. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 82, 90-92, 140-148, 150-155, 157-160 and 162-164 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a rejection for lack of written description.

This rejection maintains the reasons of record as set forth in the previous Office action and is extended to claims not previously rejected for lacking written description.

The claims are broadly drawn to methods for inducing a biological response in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements (see claim 1). The specification (at p. 27, lines 18-20) contemplates, methods wherein the multivalent ligands of the instant invention are useful "for controlling or modulating the effect of chemical signals in a biological system." The specification, at p. 27, lines 19-23, states that the instant disclosure exemplifies application of "multivalent ligands to bacterial and eukaryotic chemotaxis, to migration of leukocytes (particularly neutrophils), to immune responses of B-cells and T-cells, to cell aggregation, and to signaling of apoptosis." Actual working embodiments (specification at p. 45, line 21-p. 50, line 27 and pp. 60-64, Scheme 1-Scheme 5) involve saccharide ligands for chemotaxis in *E. coli* and concanavalin A-mediated agglutination in Jurkat T cells and erythrocytes and PC12 cell cytotoxicity experiments.

The specification does not describe a sufficient number of species of responses induced by multivalent ligands to be representative of the genus of intracellular signals and/or the vast genus of biological responses.

Vas-Cath Inc. v. Mahurkar, 19 USPQ 2d 1111, 1117, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

To provide adequate written description and to provide evidence of possession of a claimed genus, the specification must provide a representative number of species. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus and describe sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and / or chemical properties, functional characteristics, structure / function correlation, methods of making the claimed product, and combinations thereof.

The broad genus of methods inducing a biological responses using multivalent ligands admits to substantial variation that would include virtually any biological response. The specification exemplifies five general categories (chemotaxis, leukocyte migration, immune response, cell aggregation and apoptosis) and provides working examples of as few as two multivalent ligands (a saccharide and concanavalin A). The specification describes an intracellular signal transduction system that is a two component found in prokaryotes. The examiner respectfully submits that the examples are not so comprehensive as to be representative of the full scope of the claimed genus. The specification does not disclose that N-formyl peptides act as mitogens, or that they effect the release of calcium as an intracellular signal, as in claims 152 and 153. Furthermore, the rejected claims recite little molecular structure or identity for the receptors, signal recognition elements, or molecular scaffold. Accordingly, the specification does not provide adequate written description of the claimed genus of

methods inducing biological responses, comprising receptors, ligands, and molecular scaffolds.

The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of all multivalent ligands that bind to any receptor to induce any biological response, and given the few actual examples provided and the unpredictability of the ligand-receptor and medicinal drug art, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making and using multivalent ligands. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The multivalent ligands themselves are required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, at 1483 (finding claims directed to *mammalian* FGF's were found to be unpatentable due to lack of written description for that broad class, where the specification provided only the *bovine* sequence).

Therefore, only the methods comprising specific multivalent ligands that bind to cellular receptors to induce chemotaxis or agglutination, as taught by the instant specification, but not the full breadth of the claim, meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Response to Arguments

Applicant argues the formulas, structures, examples and description regarding synthesis of the ROMP-based multivalent ligands containing n-formyl and N-acyl peptides provide a written description that is sufficient in view of what is known in the art about such polymers and derivatized peptides that the skilled artisan would consider that the applicant was in possession of the invention as now claimed at the time the application was filed, (Reply at p. 23, para 1). Applicant points to p. 40 of the specification for the teaching that N-formyl peptides function as chemoattractants and that certain cells release "*intercellular* signals that affect responses in other cells and that this is particularly observed in immune systems cells" [emphasis added], (Reply at p. 20, para 2). Applicant points statements found in the specification at pp. 9, 15-16, teaching N-formyl peptides or N-acyl peptides as inducing the release of signals from cells, (see Reply at p. 21). Applicant argues that if the statements are considered reasonable to support enablement, they should be sufficiently reasonable to also support written description.

Applicant's arguments entered 12/13/2005 have been fully considered but they are not persuasive. Applicant's arguments regarding *intercellular* signals do not address claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 82, 90-92, 140, 142, 143, 148, 150-155, 157, and 162-164, drawn to *intracellular* signals. The examples and teachings that applicant points to for intercellular signal systems between cells, do not

provide a representative number of species to adequately describe the vast genus of any "biological response", as in claims 141, 144-147, and 158-161.

In regard to applicant's argument that if the statements are considered reasonable to support enablement, they should be sufficiently reasonable to also support written description, the examiner respectfully resubmits that "Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115)", (as stated in the previous Office action).

Maintained Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

17. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 66, 68, 71-74, 82, 83, 90-92,140-143, 144, 148, 150, 151, 154, 155, 157, 159, 162-164 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Whitesides** et al., WO 98/46270 (reference 4, IDS filed 10/10/2002), **Arimoto** et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11), and further in view of **Painter** et al., Journal of Cell Biology, 1987, vol. 105, pp. 2959-2971 (of record).

This rejection maintains the reasons of record as set forth in the previous Office action. This rejection is extended to claims newly added by amendment. The rejection is copied below for the convenience of the reader.

The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand comprising a plurality of signal recognition elements wherein the signal recognition elements are recognized by at least one of the receptors and

wherein the signal recognition elements are bonded to molecular scaffold, and wherein the signal recognition element is a derivatized peptide and is an N-formylated peptide, as in claims 66, 84 and 150.

Whitesides et al., teach methods for inducing a biological response using multivalent ligands, including ligands where the signal recognition element is a peptide, as presented above.

Arimoto et al., teach methods for inducing a biological response by multivalent ligands having the structure as formulated as in claim 144, as presented above.

Neither of Whitesides et al. or Arimoto et al., as above, teach methods for inducing a biological response by multivalent ligands, wherein the signal recognition element is a derivatized peptide and is an N-formylated peptide.

Painter et al., teach a derivatized peptide that is an N-formylated peptide that is a ligand that binds to a glycoprotein receptor and acts as a recognition element to stimulate chemotaxis of human neutrophils.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to combine methods of comprising inducing biological response by multivalent ligands that bind to receptors, wherein such methods comprise ligands with derivatized or N-formylated peptides.

One of ordinary skill in the art would have been motivated to use methods comprising derivatized or N-formylated peptides in multivalent ligands in order to stimulate chemotaxis of human neutrophils, as taught by Painter et al. One of ordinary skill in the art would have had a reasonable expectation of success, because N-formylation of peptides was long known in the art, as was the formylated peptide induction of neutrophil chemotaxis.

Response to Arguments

Applicant argues that the reference of Whitesides et al. does not specifically disclose multivalent ligands containing N-formyl peptides and no specific disclosure of the use of such ligands for inducing the release of a signal from a cell. Applicant argues that there is no specific enabling teaching of the use of any polymer presenting N-formyl peptides in the reference of Whitesides et al.

Applicant argues that the reference of Arimoto et al. does not teach or suggest that any strengthening of the binding interaction by use of a polyvalent species would have any beneficial effect on the induction of an intracellular signal by N-formyl peptides.

Applicant argues that the reference of Painter et al. does not teach or suggest that any polymer containing an N-formyl peptide would retain the function of the N-formyl peptide to stimulate chemotaxis of human neutrophils and further that there is no

teaching that any benefit could be obtained by presenting an N-formyl peptide to the neutrophil in a polyvalent manner.

Applicant's arguments entered 12/13/2005, have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Whitesides et al. teach the making and use of multivalent ligands produced by ROMP technology, and wherein the ligand can be a peptide. The reference of Arimoto teaches the use of multivalent ligands produced by ROMP technology, including the particular structures of claims 144 and 162. The reference of Painter et al. teaches and suggests that N-formyl oligopeptides as members of a class of peptides which initiate a variety of rapid biochemical and cellular responses that include the positive chemotaxis of human neutrophils. Absent objective evidence to the contrary, there would have been a reasonable expectation of success in making multivalent ligands comprising N-formyl peptides, because Whitesides et al. teach that the ligand can be a peptide, and Painter et al. teaches that N-formyl peptides are a class of peptides. Applicant offers no objective evidence, notwithstanding arguments of counsel, that N-formyl peptides would not be considered suitable by one of ordinary skill in the art, for use in multivalent ligand

compounds for inducing a variety of biochemical and cellular responses, including chemotaxis of human neutrophils.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 17, 21, 22, 28-30, 41, 42, 59, 60, 64, 68, 74, 82, 90, 91, 92, 142, 143, 144, 150, 151, 154, 155, 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Gordon et al.**, Chemistry & Biology, vol. 7:9-16, 2000 (of record), in view of **Schiffman et al.**, US 4,427,660.

The claims are drawn to methods for inducing a biological response in a biological system comprising one or more receptors wherein a multivalent ligand

comprising a plurality of signal recognition elements bonded to molecular scaffold and wherein the signal recognition elements are recognized by at least one of the receptors, wherein one or more of the signal recognition elements is an N-formyl peptide, and variations thereof.

Gordon et al., throughout the publication and at the abstract, p. 9, para 4-p. 10, para 2, teach using ring-opening metathesis polymerization (ROMP) to generate to form multivalent arrays that include multivalent ligands for binding to cell surface receptors; teach at Figures 3-5, polymers of the general formula of claims 82, 91 (e.g., m=0 and n=2 or more) and 144; at p. 13, para 2 and 3, teach multivalent ligands coupled to a fluorescent reporter group that is fluoresce in, where the signal recognition element binds to L-selectin, which acts to recruit white cells to sites of tissue damage, and so acts as a guide to cells, i.e., chemoattractant, as demonstrated on human T-cells (Jurkat cells).

Gordon at p. 9, para 2 and 3 teaches that attachment of assemblage of biologically active multivalent ligands, and that multivalent recognition events have importance in biology. Gordon at p. 10 teaches ligands that target selectins and that selectins are cell-surface proteins that facilitate the recruitment of leukocytes to sites of inflammation, that selectins have been inhibited with multivalent ligands, and that multivalent ligands have greater potency than monovalent counterparts. Gordon at p. 10-p. 11, bridging paragraph, and p. 13, para 4, cites references showing that L-selectin recruitment of white blood cells to cites of inflammation was known in the art and teaches a neoglycopolymer bearing a 3,6-disulfogalactose epitope (as in claim 86),

such as compound **11a** and its reporter derivative, compound **16**, (see also Fig. 5) as multivalent ligands of L-selectin. Also, the instant Specification states: "Most non-self proteins and many carbohydrates are antigens, so epitopes, without limitation, proteins fragments (e.g., peptides) and carbohydrate fragments (e.g., saccharides and oligosaccharides)." Specification at p. 15, line 26-29. Therefore, the saccharide ligands taught by Gordon are epitopes. Gordon at pp. 13-14, bridging paragraph, states the multivalent ligands taught have biological activities that range from their function as effective inhibitors of the selectins to molecules that promote L-selectin downregulation from the cell surface. Gordon at p. 13, para 3-4, teaches neoglycopolymer reporter ligand **16** as binding Jurkat cells, and teaches that these neoglycopolymers inhibit L-selectin-mediated cell rolling. Gordon at p. 10, para 2 and p. 11, para 1, teaches that selectins recruit leukocytes to sites of inflammation, reading on chemoattraction (as in claim 85) and that selectins are mucin-like proteins that present multiple copies of anionic saccharide epitopes, and that neoglycopolymers, such as compound **11**, mimic mucins, and inhibit selectins by adopting structures similar to selectins, so that, absent evidence to the contrary, the multivalent ligands comprising compounds **11** and **16**, further mimic the chemoattractant properties of selectins.

The reference of Gordon et al. does not disclose N-formyl peptides.

Schiffman et al., US 4,427,660, throughout the patent, teach the use of certain N-formyl tri- and tetra- peptides as chemoattractants, and in covalent conjugation with antibiotics. Thus Schiffman et al. teach the use of conjugates, reading on multivalent compounds, which comprise a class of N-formyl peptides, particularly as medicinals and

drugs (col.s 2, 4), in covalent combination with antibiotics. Schiffman et al. teach these N-formyl peptides as having a binding site on leukocytes, (col. 5, lines 45-49), and that these binding sites are cell surface receptors (e.g., col. 12, lines 22-30).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for inducing the release of an intracellular signal by a cell in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements bonded to a molecular scaffold, wherein the scaffold is a ROMP scaffold and wherein one or more of the signal recognition elements is an N-formyl peptide.

One of ordinary skill in the art would have been motivated to use N-formyl peptides as signal recognition elements in a multivalent ligand because Schiffman et al. teach the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils. One of ordinary skill in the art would have been motivated to use multivalent ligands with a ROMP scaffold, because Gordon et al. and Arimoto et al. teach such scaffolds for the purpose of making multivalent ligands.

One of ordinary skill in the art would have had a reasonable expectation of success in using N-formyl peptides as part of a multivalent system because Schiffman et al. teach the making and using N-formyl peptides in combination with antibiotics to produce pharmaceuticals.

19. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 82, 90-92, 140-143, 151, 154, 155, 157 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Whitesides** et al., WO 98/46270 (reference 4, IDS filed 10/10/2002), in view of **Schiffman et al.**, US 4,427,660.

Whitesides, throughout the publication and at p. 3, lines 11-24, p. 7, lines 24-31, p. 14, lines 1-9, p. 15, lines 20-31, teaches multivalent ligands on a polymeric backbone of the form $Y-(A)_n$, where Y is a framework, A is a functional group, and n is an integer greater than 10, 50 or more, or about 100 or more and wherein the functional group that is a signal recognition is covalently bonded to the framework that is a molecular scaffold, such as a liposome; teaches at p. 32, lines 7-13, polyvalent presenters that include Sialyl Le^x that bind leukocyte receptor sites including integrins and selectins and are elements involved in signal recognition, inducing intracellular and intercellular responses; teaches at p. 60, line 26-p.61, line 20 modulation of cell-cell interactions by polyvalent presenters, (which include multivalent ligands), whereby numerous cell-cell interactions can be promoted or inhibited, such as neutrophil attachment to endothelial cells during inflammation; teaches at Table 2, p. 62, line 4-p. 63, line 7, cell-cell interactions that comprise neutrophil, endothelial cells, T–cells, and the release of platelet granules; at p. 87, lines 3-18, teaches cytokine production by replacing a stimulator cell in a cell-cell interaction that normally leads to cytokine secretion, e.g., using L-selectin ligands to simulate monocytes and macrophages to produce tumor necrosis factor; teaches at p. 96, line 1-p. 99 line 16, *in vitro* assays; at p. 97, line 31- p.

99, line 16, teaches cross-linking multivalent receptors on the cell by agglutinins to prevent the biological response of viral binding to the cell surface.

Whitesides, for example, at p. 118-120, Example 5, p. 141, Figure 11, teaches methods for facilitating the treatment of influenza by inhibiting influenza-mediated hemagglutination comprising multivalent ligands of the formulas of claims 82 and 91 (where m=0 and n=2 or more), where SRE is NeuAc connected by a linker to a backbone repeating unit that is acyclic, R4-R6 are organic groups, and Z is H or an organic group.

Whitesides, at p. 93, line 18-p. 94, 12, teaches an intracellular signal transduction mechanism triggered by activation of certain G-protein coupled receptors that that mediates intracellular signal transduction (as in claims 18 and 19) and results in a reaction of the acrosomal exocytosis of sperm.

Furthermore, Whitesides at p. 4, lines 7-17, teaches, for example, methods for treating a disease or condition using polyvalent ligands, which read on effecting a biological response; or for treating a number of disease, Whitesides at p. 94, line 22-p. 95, line 9.

Whitesides, for example at p. 61, states that polyvalent presenters (reading on multivalent ligands) can be used to modulate cell-cell interactions and that numerous biological processes require cell-cell interaction that can be promoted or inhibited, and at Table 2, p. 62, list cells whose biological response may be so affected, said cells including neutrophils, endothelial, and cells, as in claims 20-23 and 30. Whitesides, for example at p. 94, lines 7-12, teaches an intracellular signal transduction mechanism

triggered by activation of certain G-protein coupled receptors that results in a reaction of the acrosome of sperm, and at p. 94, lines 1-21, teaches using multivalent GlcNac ligands to induce acrosomal exocytosis of mouse sperm, that involves an intracellular signal, as in claims 28, 29, 154 and 155. Whitesides, for example at p. 87, lines 3-18, teaches the modulated release of cytokines by polyvalent ligands, as in claim 155. Whitesides, for example at p. 94, lines 7-8, teaches reorganization of cell surface receptors involved in fertilization, which reads on modulating a biological response, or at p. 97, line 31-p.99, line 15, teaches crossing linking multivalent receptors to prevent viral binding to cell surfaces, as in claims 41 and 42. Whitesides at p. 36, lines 9-22, teaches polyvalent ligands on solid supports, such as beads, that are useful in screening for a adhesion, or adhesion resulting in, for example, infection, cell death, cell proliferation, morphological change, etc., as in claim 140. Therefore, Whitesides et al., throughout the patent teach the claimed invention, as set forth above and in the previous Office action.

The reference of Whitesides et al. does not disclose N-formyl peptides.

Schiffman et al., US 4,427,660, throughout the patent, teach the use of certain N-formyl tri- and tetra- peptides as chemoattractants, and in covalent conjugation with antibiotics. Thus Schiffman et al. teach the use of conjugates, reading on multivalent compounds, which comprise a class of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4), in covalent combination with antibiotics. Schiffman et al. teach these N-formyl peptides as having a binding site on leukocytes, (col. 5, lines 45-49), and that these binding sites are cell surface receptors (e.g., col. 12, lines 22-30).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for inducing the release of an intracellular signal by a cell in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements bonded to a molecular scaffold, wherein the scaffold is a ROMP scaffold and wherein one or more of the signal recognition elements is an N-formyl peptide.

One of ordinary skill in the art would have been motivated to use N-formyl peptides as signal recognition elements in a multivalent ligand because Schiffman et al. teach the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils. One of ordinary skill in the art would have been motivated to use multivalent ligands with a ROMP scaffold, because Whitesides et al. teach such scaffolds for the purpose of making multivalent ligands.

One of ordinary skill in the art would have had a reasonable expectation of success in using N-formyl peptides as part of a multivalent system because Schiffman et al. teach the making and using N-formyl peptides in combination with antibiotics to produce pharmaceuticals.

20. Claims 17, 21-23, 28, 82, and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Kiessling** et al., US 6,291,616, (reference 1, IDS filed 10/10/2002), in view of **Schiffman et al.**, US 4,427,660.

Kiessling et al., US 6,291,616, at col. 1, lines 10-48, teach using ring-opening metathesis polymerization (ROMP) to generate to form multivalent arrays that include multivalent ligands for binding to cell surface receptors, e.g. through epidermal growth factor, resulting in dimerization of the transmembrane receptor; teaches at col. 10, line 32-col. 11, line 46, polymers of the general formula of claims 82 and 91, col. 13, line 44-col. 14, line 32, teach multivalent ligands coupled to a fluorescent reporter group that is fluoresce in, where the signal recognition element binds to L-selectin, which acts to recruit white cells to sites of tissue damage, and so acts as a guide to cells, i.e., chemoattractant, as demonstrated on human T-cells (Jurkat cells).

Kiessling at col. teaches coupling an amine-containing saccharide moiety to yield a 3,6-disulfogalactose derivative to form neoglycopolymers. Kiessling at col. 13, lines 51-60, teaches that L-selectin facilitates the recruitment of white blood to sites of tissue damage and that these neoglycopolymers inhibit selectin function by binding to L-selectin on the cell surface. Kiessling at col. 14, lines 5-19, teaches that these neoglycopolymers bind to Jurkat cells, and at col. 14, lines 20-27, state: "Moreover, further microscopy studies suggest that the significant biological activities of these glycoprotein mimics are mediated through multivalent contacts." Thus Kiessling teaches methods comprising glycopolymer multivalent ligands that induce a biological response, as in the claimed invention. The term "biological response" is very broad and the specification and the claims do not provide a specific, limiting definition for the term

The reference of Kiessling et al. does not disclose N-formyl peptides.

Schiffman et al., US 4,427,660, throughout the patent, teach the use of certain N-formyl tri- and tetra- peptides as chemoattractants, and in covalent conjugation with antibiotics. Thus Schiffman et al. teach the use of conjugates, reading on multivalent compounds, which comprise a class of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4), in covalent combination with antibiotics. Schiffman et al. teach these N-formyl peptides as having a binding site on leukocytes, (col. 5, lines 45-49), and that these binding sites are cell surface receptors (e.g., col. 12, lines 22-30).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for inducing the release of an intracellular signal by a cell in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements bonded to a molecular scaffold, wherein the scaffold is a ROMP scaffold and wherein one or more of the signal recognition elements is an N-formyl peptide.

One of ordinary skill in the art would have been motivated to use N-formyl peptides as signal recognition elements in a multivalent ligand because Schiffman et al. teach the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils. One of ordinary skill in the art would have been motivated to use multivalent ligands with a ROMP scaffold, because Kiessling et al. teach such scaffolds for the purpose of making multivalent ligands.

One of ordinary skill in the art would have had a reasonable expectation of success in using N-formyl peptides as part of a multivalent system because Schiffman

et al. teach the making and using N-formyl peptides in combination with antibiotics to produce pharmaceuticals.

21. Claims 17, 21-23, 28, 59, 60, 64, 68, 74, 82, 90-92, 144, 148, 150, 154, 155, 157, 159, 162, 163, and 164 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Arimoto** et al., Chem. Commun., July 1999, Vol. 15, 1361-1362, (IDS filed 10/10/2002, ref. 11), in view of **Schiffman et al.**, US 4,427,660.

Arimoto et al., throughout the publication and Figures and Scheme 1, teach methods for inducing antibacterial activity by introducing a multivalent ligand comprising a plurality of vancomycin residues, reading on signal recognition elements bonded to a ROMP-derived molecular scaffold of the formula of claim 82, that binds to D-Ala-D-Ala residue of the pentapeptide terminal of biosynthetic intermediates, which, absent evidence to the contrary, reads on a receptor of bacteria. Arimoto teaches at Scheme 1, polymers of the general formula of claims 82, 91 (where m=0 and n=2 or more) and 144.

The reference of Arimoto et al. does not disclose N-formyl peptides.

Schiffman et al., US 4,427,660, throughout the patent, teach the use of certain N-formyl tri- and tetra- peptides as chemoattractants, and in covalent conjugation with antibiotics. Thus Schiffman et al. teach the use of conjugates, reading on multivalent compounds, which comprise a class of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4), in covalent combination with antibiotics. Schiffman et al. teach these

N-formyl peptides as having a binding site on leukocytes, (col. 5, lines 45-49), and that these binding sites are cell surface receptors (e.g., col. 12, lines 22-30).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for inducing the release of an intracellular signal by a cell in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements bonded to a molecular scaffold, wherein the scaffold is a ROMP scaffold and wherein one or more of the signal recognition elements is an N-formyl peptide.

One of ordinary skill in the art would have been motivated to use N-formyl peptides as signal recognition elements in a multivalent ligand because Schiffman et al. teach the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils. One of ordinary skill in the art would have been motivated to use multivalent ligands with a ROMP scaffold, because Arimoto et al. teach such scaffolds for the purpose of making multivalent ligands.

One of ordinary skill in the art would have had a reasonable expectation of success in using N-formyl peptides as part of a multivalent system because Schiffman et al. teach the making and using N-formyl peptides in combination with antibiotics to produce pharmaceuticals.

22. Claims 17, 21-23, 28, 59, 60, 64, 68, 74, 82, 90-92, 144, 148, 150, 152, 154, 155, 156, 157, 159, 162, 163, and 164 are rejected under 35 U.S.C. 103(a) as being

unpatentable over **Kanai** et al., J. Am. Chem. Soc, 1997, Vol. 119 (41), pp. 1361-1362, (IDS filed 10/10/2002, ref. 45), in view of **Schiffman et al.**, US 4,427,660.

Kanai et al., throughout the publication, teach methods for inducing interference with erythrocyte agglutination mediated by the carbohydrate-binding protein concanavalin A by introducing multivalent ligands which posses a plurality of saccharide residues, which read on a plurality of signal recognition elements, that are covalently bonded (as in claim 74) to a ROMP-derived scaffold of the formula in claim 82. Kanai, at Table 1, teach more than 100 repeating units in the neoglycopolymer, as in claims 71-73. Kanai et al. teaches at Figure 1, polymers of the general formula of claims 82, 91 (where m=0 and n=2 or more) and 144. Concanavalin A induces an intracellular signal by increasing Ca^{2+} concentration in the cell, as evidenced by Ramaschi et al., (IDS filed 10/10/2002, ref. No. 76).

The reference of Kanai et al. does not disclose N-formyl peptides.

Schiffman et al., US 4,427,660, throughout the patent, teach the use of certain N-formyl tri- and tetra- peptides as chemoattractants, and in covalent conjugation with antibiotics. Thus Schiffman et al. teach the use of conjugates, reading on multivalent compounds, which comprise a class of N-formyl peptides, particularly as medicinals and drugs (col.s 2, 4), in covalent combination with antibiotics. Schiffman et al. teach these N-formyl peptides as having a binding site on leukocytes, (col. 5, lines 45-49), and that these binding sites are cell surface receptors (e.g., col. 12, lines 22-30).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have used methods for inducing the release of an

intracellular signal by a cell in a biological system by introducing a multivalent ligand comprising a plurality of signal recognition elements bonded to a molecular scaffold, wherein the scaffold is a ROMP scaffold and wherein one or more of the signal recognition elements is an N-formyl peptide.

One of ordinary skill in the art would have been motivated to use N-formyl peptides as signal recognition elements in a multivalent ligand because Schiffman et al. teach the use of N-formyl peptides for the chemotaxis of leukocytes, including neutrophils. One of ordinary skill in the art would have been motivated to use multivalent ligands with a ROMP scaffold, because Kanai et al. teach such scaffolds for the purpose of making multivalent ligands.

One of ordinary skill in the art would have had a reasonable expectation of success in using N-formyl peptides as part of a multivalent system because Schiffman et al. teach the making and using N-formyl peptides in combination with antibiotics to produce pharmaceuticals.

Conclusion

23. Claims 17, 20-23, 28-30, 41, 42, 59, 60, 64, 68, 71-74, 82, 90-92, 140-148, 150-155, and 157-164 are rejected. No claims are allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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